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(54) SYNERGISTIC EFFECT OF ADENYLIC NUCLEOTIDES IN DIGITALIS THERAPY

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This invention relates to cardiac therapy. More particularly, this invention relates to the synergistic effects of adenylic nucleotides on the use of digitalis in cardiac therapy.

Whole-leaf digitalis and the purified cardiac glycoside derivatives of digitalis lanata and digitalis purpurea, e.g, digitoxin, digoxin, lanatoside A, and the like, have long been considered the most effective medicinal agents in cardiac therapy. The loss of cardiac reserve manifested by congestive heart failure is the result of an imbalance between cardiac muscle strength and the work load imposed on the heart. Therapy is therefore usually directed toward improving the function of the failing heart muscle and reducing the work load on the myocardium. The digitalis drugs are the only commonly known agents which restore compensation through direct action on the myocardium.

The major pharmacologic effect of digitalis is its direct action on the myocardium. Digitalis increases the force of systolic contractions of the heart muscle, without alteration in the diastolic fiber size. The more forceful contraction results in more complete ventricular emptying with a rise in volume output. There is also an enhanced capacity to propel blood against increased peripheral resistance. At the same time the duration of systole is abbreviated, allowing greater time for both ventricular filling and heart rest. The diastolic size of the heart is reduced. Since oxygen consumption is a function of the initial fiber length such a reduction in size diminishes the oxygen expenditure for any work output. The work capacity of the heart is thereby increased and a greater percentage of the liberated energy is used in mechanical processes of shortening and development of tension. The overall

effect of digitalis appears to be a more efficient utilization of phosphate bond energy with a resulting increas in cardiac efficiency and output. The basic pattern of myocardial derangement that characterizes failure is thus reversed. In other words, the digitalized failing heart can do the same work with less energy, i.e., oxygen utilization, or more work with the same energy expediture than before digitalization.

The major problem associated with digitalis therapy is the toxic manifestation of the drug which results from overdosage. Although overdosage is usually not a major problem in most therapeutic treatments, it is an ever present danger in digitalis therapy due to the prevalent practice of administering digitalis until the first appearance of toxic manifestations. Some of the early toxic manifestations are easily recognized and are reversible and thus unimportant. Other manifestations of digitalis overdosage are less frequently recognized; continuation of the drug in such circumstances can lead to structural cardiac changes that are not reversible or to fatal disturbance of the cardiac mechanism.

The toxic effects of digitalis are not side effects of the drug. They are direct manifestations of excessive saturation with the drug. The most common toxic effects of all digitalis preparations are gastro-intestinal, e.g., anorexia, nausea, vomiting and the like. Lower abdominal cramps are usually the first complaint, with or without diarrhea, and these can occur in the absence of nausea or vomiting. Parenteral administration is as effective as oral administration in producing the gastro-intestinal symptoms.

Other toxic manifestations of digitalis therapy have their source in disturbances of the central nervous system. Initially, the patient may complain of fatigue, unusual drowsiness, headache or restlessness. Further

administration of digitalis can result in an increase of restlessness, periods of disorientation, occasionally an attack of delirium. Many varieties of visual disturbances can also result as cerebral toxic effects, e.g., dimness of vision, diplopia, difficulty in focusing the eyes, scotomata, yellow or green vision. In the late stages of poisoning, the patient may lapse into coma and die shortly thereafter.

Digitalis overdosage, in itself, can aggravate failure of a diseased heart through functional disturbance of ectopic rapid heart action. Moreover, overdosage can promote failure through interference with conduction or by reduction of the coronary blood flow. Due to the direct action of digitalis on the myocardium, overdosage increases myocardial irritability leading to disturbance in rhythm and structural damage to the myocardium.

There are two major difficulties in the use of digitalis. One is the wide variation in potency, absorption rates, and rates of elimination of the many digitalis preparations. The other is the wide range of individual susceptiblity to the drug. These wide differences in individual tolerance make it necessary to depend not merely on dosage, but also upon the effect produced in each individual patient. Adherence to a routine dosage schedule can result in inadequate digitalization of some patients and the poisoning of others. In most cases, digitalis is administered initially in a "digitalizing" dose which need not exceed 2.0 grams of the whole-leaf preparation or 2.0 milligrams of a purified glycoside derivative. Thereafter, smaller daily maintenance doses are administer d. While the initial digitalizing dose is nontoxic to a large majority

of patients, the daily maintenance dose often leads to excessive accumulation of the drug in the tissues. The particularly slow rate of elimination of the purified glycosides is not only a factor which produces accumulation but also leads to unusually delayed dissipation of toxic effects after the drug is discontinued. Nevertheless, digitalis and its purified glycoside derivatives are widely employed in cases of congestive heart failure, auricular flutter, auricular fibrillation, paroxysmal auriculartachycardia, hypertensive or valvular heart disease, cardiac enlargement, myocardial infarction, and the like.

Accordingly, it is an object of this invention to provide therapeutic agents which synergistically decrease the dosage requirements of digitalis.

It is another object of this invention to eliminate the toxic manifestations which are characteristic of digitalis therapy.

In accordance with the present invention, it has been found that preparations containing adenylic nucleotides, perferably adenosine-2'(3')-monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, as well as those compounds prepared by reacting procaine, nicotinamide and iron with the related adenosine monophosphoric, diphosphoric and triphosphoric acids have unexpected therapeutic value in digitalis treatment of cardiac disorders. Moreover, it has been found that when the therapeutic compositions of the present invention are administered to patients undergoing digitalis therapy, a synergistic decrease in the dosage of digitalis is afforded, thereby eliminating the toxic manifestations concomitant with digitalis overdosage or accumulation

It has been found that a safe and satisfactory therapeutic dosage of the adenylic nucleotides useful in

this invention can range from about 25 milligrams up to about 300 milligrams per dosage unit. The preferred dosage unit contains an adenylic nucleotide, preferably adenosine-2'(3')-monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine, 3,5-phosphate, nicotinamide adenylate, procaine adenylate, iron adenylate, and the like, in an amount of from 50 to 200 milligrams. The especially preferred adenylic nucleotides are nicotinamide adenylate and procaine adenylate because they afford the quickest and most lasting relief of cardiac failure symptoms.

The preparations of the present invention can be administered orally, sublingually, parenterally or by suppository with sublingual administration being preferred because of the simplicity of treatment. It has been found, however, that treatment begun by injection results in more rapid relief.

In sublingual oral or rectal administration, the above dosage units are given four times daily. In parenteral administration, intramuscular or intravenous injections are usually given twice daily.

Clinical tests have been made utilizing the adenylic nucleotides described above in the treatment of coronary diseases as hereinbefore described and it was found that smaller, non-toxic doses of digitalis preparations could be employed to control cardiac conditions if administered in combination with an adenylic nucleotide in the dosages described. Moreover, it was found that a large dose, i.e, about 100-300 mgs. of an adenylic nucleotide preferably either procaine adenylate or nicotinamide adenylate could be administered in lieu of the initial digitalizing dose subsequently followed by maintenance doses of digitalis, i.e, less than about 1 mg. and preferably from about 0.25 -0.5 mg. and between about 50-200 mg. of an adenylic nucleotide. Because of the synergistic decrease in

digitalis with the adenylic nucleotides of the present invention, digitalis poisoning has been substantially eliminated.

In the treatment of coronary diseases, it is considered preferable to administer the adenylic nucleotide in combination with a digitalis preparation, at the onset of the attack, in 1 ampul dosages intramuscularly twice daily for about a week and thereafter 1-2 tablets four times daily sublingually. The adenylic nucleotides in combination with a digitalis preparation can also be administered intravenously in 1/2 to 1 ampul dosages suitably diluted in physiological saline solutions or the like as directed above. The adenylic nucleotides described above can be used as a supplement to or in conjunction with the conventional digitalis preparations normally administered to relieve coronary disorders. When so employed, the adenylic nucleotides synergistically decrease the digitalis dosage requirements both in the initial digitalizing dose and the subsequent maintenance dosages. In some instances, a large dose of an adenylic nucleotide can be employed in lieu of the initial digitalizing dose followed by smaller maintenance doses of a digitalis preparation supplemented by an adenylic nucleotide. Thus, the adenylic nucleotides employed in the present invention can be administered before, after or with digitalization to synergistically decrease the initial digitalizing dose to an amount insufficient, in itself, to cause digitalization and in some cases eliminate it. After digitalization, the adenylic nucleotides are also useful in decreasing the maintenance dosages of digitalis thereby preventing accumulation of the digitalis preparations in the system and hastening elimination of the purified glycosides to dissipate the toxic effects after the drug is discontinued. It has also been found that th adenylic nucleotides are useful in reducing the toxic manifestations of a host already afflicted with digitalis poisoning. The use of the adenylic nucleotides d scribed above

in this manner has been found to result in a rapid and long lasting amelioration of pain and other cardiac symptoms. Moreover, there are no unpleasant side affects due to the toxicity or instability of the preparations as were heretofore prevalent.

When the therapeutic preparations of this invention are administered parenterally, they are usually given in combination with a pharmaceutical carrier. Suitable pharmaceutical carriers which can be employed include water, physiological saline solutions and the like.

In the tablet and suppository preparations of the present invention, various binding materials such as solid polyethylene glycols, waxes, fats, fatty acids and hydrogenated oils can be employed. If, however, oral administration in an entirely liquid form is desired, the binding material can be replaced by a suitable syrup base.

It is considered preferable that the orally administered therapeutic tablet consist of from about 50 to 100 parts by weight of an adenylic nucleotide, less than 1 part by weight of a digitalis preparation, from about 175 to 200 parts by weight of sugar and from about 25 to 100 parts by weight of a binding material as described above. For example, a number of nicotinamide adenylate sublingual tablets were prepared. Each tablet had the following composition:

Nicotinamide adenylate	55 mg.
Digoxin	0.5 mg.
Sugar	190 mg.
Polyethylene glycol (1)	75 mg.
Flavoring (oil of peppermint)	Trace
Coloring (Pure Food and Drug Blue Color)	Trace

(1) Poly thylene glycol having a molecular weight between 6000 and 7500 and a viscosity of 700 to 900 centistokes at 210°F.

The total formulation per tablet varied in weight from 310 to 325 milligrams. The tablet was formulated so as to require approximately ten minutes for sublingual absorption.

Tablets and ampuls so prepared were found to be useful in conjunction with or as a supplement to digitalis preparations in the treatment of cardiac conditions.

Example I

The preferred adenylic nucleotides described herein can be prepared as follows:

a) Nicotinamide adenylate: prepared as described in U.S. 2,417,841. The powdered nicotinamide adenylate is put in appropriate pharmaceutical dosage form.

b) Adenosine-2'(3')-monophosphate, adenosine diphosphate, adenosine triphosphate, and cyclic adenosine 3,5 phosphate are commercially available. The powdered adenosine derivative or its sodium salt is put in appropriate pharmaceutical dosage form.

c) Procaine adenylate: prepared as described in Canadian Patent No. 733,963. The powdered procaine adenylate is put in appropriate pharmaceutical dosage form.

d) Iron adenylate: prepared as described in U.S. 2,215,233. The iron adenylate is put in appropriate pharmaceutical dosage form.

WHAT IS CLAIMED IS:

1. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein an adenylic nucleotide in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom; said composition being effective in the treatment of cardiac disorders.

2. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein adenosine-2'(3') monophosphate in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom; said composition being effective in the treatment of cardiac disorders.

3. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents there adenosine diphosphate in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom; said composition being effective in the treatment of cardiac disorders.

4. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein adenosine triphosphate in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which

is substantially below the tolerance l vel for toxic manifestations resulting therefrom, said composition being effective in the treatment of cardiac disorders.

5. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein cyclic adenosine 3,5 phosphate in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom, said composition being effective in the treatment of cardiac disorders.

6. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein nicotinamide adenylate in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom, said composition being effective in the treatment of cardiac disorders.

7. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein procaine adenylate in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom, said composition being effective in the treatment of cardiac disorders.

8. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the activ agents th rein iron adenylate

in combination with a digitalis preparation, said digitalis preparation being present in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom, said composition being effective in the treatment of cardiac disorders.

9. A therapeutic composition prepared for administration into the human organism comprising a pharmaceutical carrier and as the active agents therein, from about 25 to 300 milligrams per dosage unit of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5-phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, and a digitalis preparation in combination therewith in an amount per dosage unit which is substantially below the tolerance level for toxic manifestations resulting therefrom, said composition being effective in the treatment of cardiac disorders.

10. A therapeutic composition prepared for injection into the human organism comprising a pharmaceutical carrier, and as the active agents therein, from about 100 to 300 milligrams per dosage unit of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, in combination with a digitalis preparation in an amount per dosage unit insufficient, in itself, to cause digitalization, said composition being effective in the treatment of cardiac disorders.

11. A therapeutic composition prepared for injection into th human organism comprising a pharmaceutical

carrier, and as th active agents therein, from about 50 to 200 milligrams per dosage unit of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, in combination with less than about 1 milligram of a digitalis preparation, said composition being effective in the treatment of cardiac disorders.

12. A therapeutic composition prepared for injection into the human organism comprising a pharmaceutical carrier, and as the active agents therein, from about 50 to 200 milligrams per dosage unit of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, in combination with about 0.25 to 0.5 milligrams of a digitalis preparation, said composition being effective in the treatment of cardiac disorders.

13. A therapeutic composition prepared for sublingual introduction into the human organism comprising a tablet containing from about 25-300 milligrams per unit dosage of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cylcic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, in admixture with a digitalis preparation in an amount per dosage unit insufficient, in itself, to cause digitalization, said composition being effective in the treatment of coronary disorders.

14. A therapeutic composition prepared for sublingual introduction into the human organism comprising a tablet containing from about 50-200 milligrams per unit dosage

of a member selected from the group consisting of adinosine-2'-(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, in admixture with less than about 1 milligram of a digitalis preparation, said composition being effective in the treatment of coronary disorders.

15. A therapeutic composition prepared for sublingual introduction into the human organism comprising a tablet containing from about 50-200 milligrams per unit dosage of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, in admixture from about 0.25-0.5 milligrams of a digitalis preparation, said composition being effective in the treatment of coronary disorders.

16. An orally administered therapeutic composition for use in the treatment of coronary disorders comprising from about 50 to 100 parts by weight of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic adenosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate and iron adenylate, less than about 1 part by weight of a digitalis preparation, from about 175 to 200 parts sugar, and from about 25 to 100 parts of a binding material.

17. A therapeutic composition prepared for introduction into the human organism in suppository form comprising a suitable suppository base and as the active ingredients therein from about 50 to 200 milligrams of a member selected from the group consisting of adenosine-2'(3') monophosphate, adenosine diphosphate, adenosine triphosphate, cyclic ad nosine 3,5 phosphate, nicotinamide adenylate, procaine adenylate, and iron adenylate, and in combination therewith

from about 0.25 to 0.5 milligrams of a digitalis preparation.